Syndrome of the month

Incontinentia pigmenti (Bloch-Sulzberger syndrome)

S J Landy, D Donnai

Incontinentia pigmenti (IP) is a rare genodermatosis and was probably first described as early as 1906 by Garrod,[1] but the credit is given to Bardach,[2] Bloch,[3] Siemens,[4] and Sulzberger[5] for defining the condition during the 1920s, although only the names of Bloch and Sulzberger feature in the eponym. It is a multisystem, ectodermal disorder accompanied by dermatological, dental, and ocular features and in a minority of cases may be associated with neurological deficit.

The typical phenotype is a result of functional mosaicism, a phenomenon which occurs in X linked dominant disorders because of lyonisation.

The name incontinentia pigmenti describes the characteristic, albeit non-specific, histological feature where there is incontinence of melanin from the melanocytes in the basal layer of the epidermis into the superficial dermis.

Genetics

Extensive pedigree review suggests X linked dominance with lethality in males. This mode of inheritance is supported by the high female:male ratio, female to female transmission, increased incidence of miscarriages and by the occurrence of two reported cases of classical IP in males with Klinefelter syndrome (47,XXY).[6,7] The half chromatid mutation model and postzygotic mutation have been suggested to explain the survival of occasional sporadic males with IP.[8,9]

In 1985 linkage to Xp11 was suggested after reports of five females with de novo X;autosome translocations involving Xp11 associated with phenotypes similar to IP.[10–13] In 1987 Happle[14] suggested that these were cases of pigmentary mosaicism rather than classical IP. Females with an IP phenotype and X;autosome translocations raise several problems. The variegated phenotype of IP depends on random lyonisation, while the pathological effects of X;autosome translocations depend on non-random lyonisation, the normal X chromosome being preferentially inactivated.

Sefiani *et al*[15] in 1988 excluded the possibility of linkage to Xp11 in a series of familial cases. In 1991, in a large linkage study involving 12 families and nine terminal X long arm markers, they confirmed linkage of familial IP to the Xq28 region with a lod score of 6·19 at a recombination fraction of 0·03.[16] This is supported by linkage analysis, done by the authors, in six pedigrees with lod scores of 3·2 for two terminal X long arm markers (unpublished data).

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Clinical features

This information is based on several accounts[17–33] and on an unpublished clinical study involving 111 patients, with clinical features compatible with familial IP, undertaken by the authors (Landy *et al*, in preparation). As would be expected in an X linked dominant disorder the presentation in female carriers is variable, presumably a result of lyonisation.

SKIN

The cutaneous manifestations of incontinentia pigmenti are diagnostic; however, their absence does not exclude the diagnosis. Classically the dermatological features are described in four stages but all stages do not necessarily occur and several stages may overlap. Stage 1: erythema, vesicles, pustules. Stage 2: papules, verrucous lesions, hyperkeratosis. Stage 3: hyperpigmentation. Stage 4: pallor, atrophy, and scarring.

Stage 1

The first stage is characterised by blisters, usually preceded by erythema, which occur anywhere on the body but usually spare the face (fig 1). The lesions of the first stage develop within the first few weeks of life. Typically the blisters appear at or soon after birth and often respect the midline (fig 2). A linear distribution, along the limbs and circumferentially around the trunk, is classically described although this is not absolute. Each crop of blisters clears within weeks and they may or may not be replaced by new crops, at the same or different sites. In general, stage 1 has cleared completely by four months. It is not uncommon for the blisters to recur during acute febrile illness in childhood but these eruptions are less severe than those seen in the neonatal period and are short lived. The initial inflammatory phase is accompanied by massive infiltration of eosinophils into the epidermis and marked peripheral blood leucocytosis with up to 65% eosinophils.

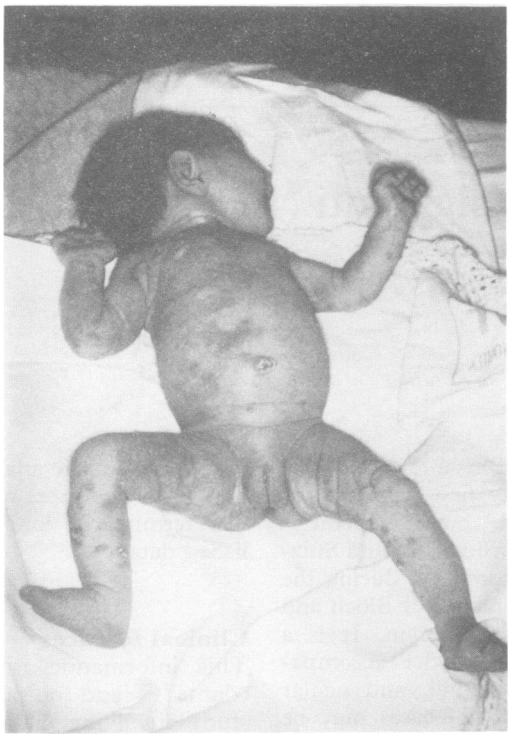

Figure 1 Stage 1 at 10 days showing linear streaks of vesicles on the trunk and limbs but sparing the face.

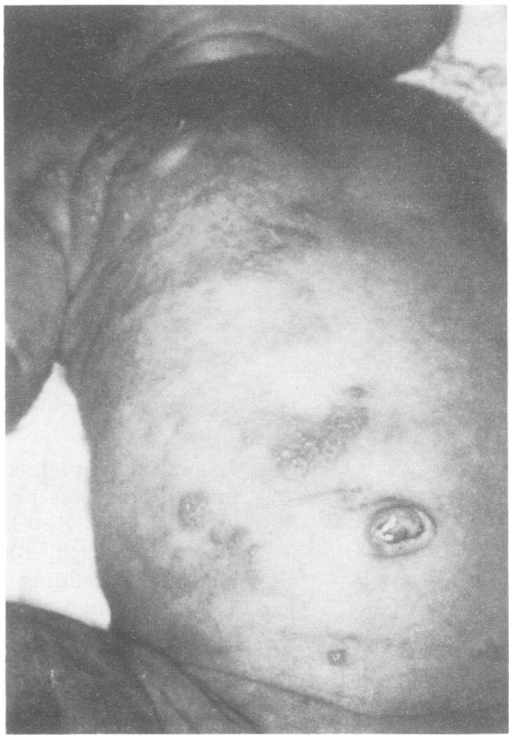

Figure 2 Vesicular lesions on the trunk respecting the midline.

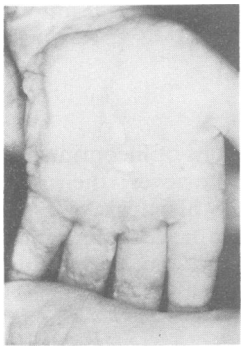

Figure 3 Stage 2 at 4 weeks showing verrucous lesions in a linear distribution on the palm.

Stage 2

The typical, hyperkeratotic lesions of stage 2 may be present from an early stage. They usually appear on the distal limbs, as the blisters begin to heal, after several weeks (fig 3). Sometimes these lesions do not occur or may be so trivial that they go unnoticed. The blisters on the distal limbs become dry and hyperkeratotic forming warty lesions which may persist (fig 4). These lesions rarely affect the trunk or face but may occur on the scalp. They clear completely by six months in over 80% of cases.

Stage 3

Stage 3 is, classically, the hallmark of IP but again its presence and extent are variable. It ranges from no or very little hyperpigmentation to extensive involvement of the skin. The hyperpigmentation fades and has disappeared by the end of the second decade. This hyperpigmentation is more often apparent on the trunk than the limbs and occurs in streaks or whorls which respect Blaschko's lines (figs 5 and 6). The nipples are frequently involved in the increased pigmentation and the axillae and groins are invariably affected. The timing of the pigmentary abnormalities varies but in general the streaks gradually appear sometime after the blisters have disappeared and become darker over weeks or months. The distribution of these lesions is often unrelated to the distribution of the previous vesicular rash. The pigmented lesions remain static for a period of time until they fade during childhood and adolescence. By the age of 16 the majority of these pigmented lesions have disappeared. Occasionally they remain and can be a permanent feature, usually in the groins. Sometimes there is no delineation between the stages and several features occur concurrently (fig 6).

Stage 4

The features of the fourth stage are those of 'burnt out' IP and are often present before the hyperpigmentation has disappeared completely. The typical lesions seen in adults and adolescents with IP are pale, hairless patches

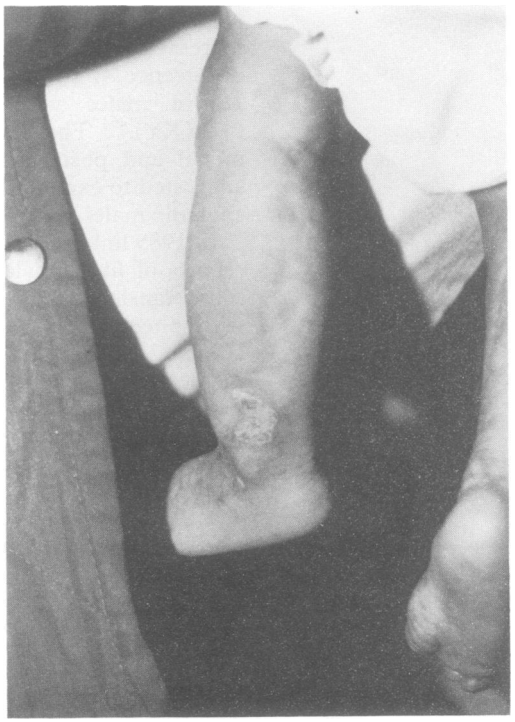

Figure 4 Persistent hyperkeratotic lesion over the lateral malleolus at 6 months.

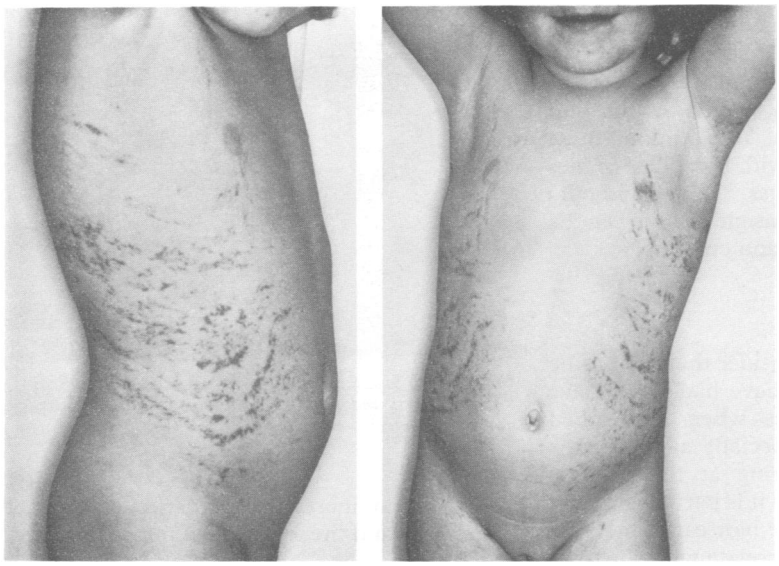

Figure 5 Stage 3 at 3 years showing classical hyperpigmentation following Blaschko's lines.

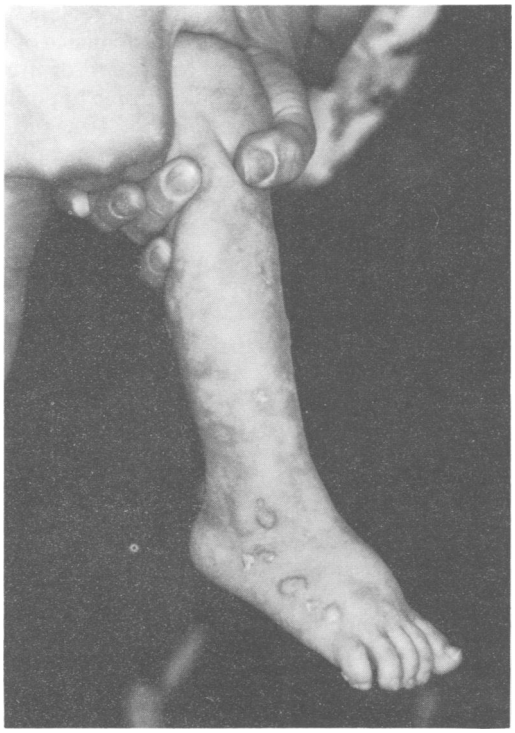

Figure 6 At 18 months this patient had evidence of stages 1, 2, and 3 with bullae, verrucae, and hyperpigmentation. There was also evidence of stage 4 with pale, atrophic lesions elsewhere.

or streaks best seen on the lower leg (fig 7). Moss and Ince[29] in 1987 first noticed that although these lesions, seen best on the posterior calves, are usually described as hypopigmented, in fact the contrast with normal skin is probably because of the lack of hair follicles and reduced vascularity and that the difference in pigmentation is a minor factor. Some subjects admit that these areas become more obvious when the normal skin tans in sunlight but some claim that the contrary is true. We support the observation of Moss and Ince[29] and this may help our understanding of the pathogenesis of the lesions seen in this disorder.

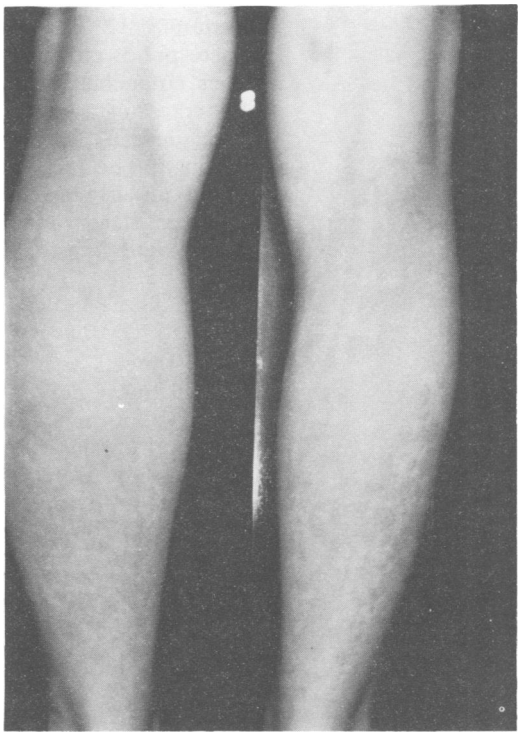

Figure 7 Stage 4 showing pale, hairless, atrophic linear lesions on the posterior lower leg. This patient also has a right hemiparesis.

The skin covering the trunk in affected adults may show atrophic linear or reticulate lesions with normal or increased pigmentation. These lesions, if present at all, tend to be less atrophic than those seen on the limbs, reflecting the degree of damage to the dermis.

NAILS

The frequency of nail dystrophy may be as high as 40% but it is usually mild. The degree of involvement is variable, ranging from mild ridging or pitting to onychogryposis and severe nail disruption not unlike onychomycosis (fig 8). Fortunately these episodes of nail disintegration seem to be temporary but may recur during childhood or adolescence. The cause of this nail disruption is unknown. If onychodystrophy is present then it is seen in all or most of the nails on the hands and the feet.

Subungual keratotic tumours associated with IP have been described by various

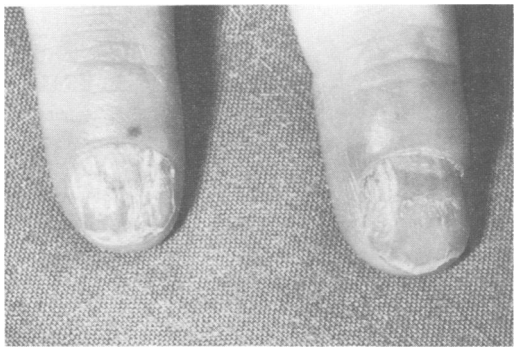

Figure 8 Severe nail dystrophy in a 3 year old girl which lasted six months and has resolved completely.

authors.[28 34-36] The histology of these tumours corresponds closely to that seen in the verrucous cutaneous lesions of stage 2 and shows hyperkeratosis, acanthosis, papillomatosis, and focal dermal dyskeratosis. In addition, these lesions can be associated with bony deformities of the underlying phalanges.[28] These tumours are painful as well as unsightly and can be eradicated by desiccation and curettage.

HAIR

Most subjects with IP consider their hair to be normal but almost 50% have had or do have minor abnormal features when questioned specifically. Alopecia, especially at the vertex and usually after blistering at this site, is common but in most cases it is partial and goes unnoticed. Thin or sparse hair early in childhood does not seem to correlate with the quality or quantity of the hair in later life. Abnormal hair in IP tends to be lustreless, wiry, and coarse and occurs, more often than not, at the vertex. Wiklund *et al*[20] first described this, calling it the woolly-hair naevus. There are very few patients with IP who have severe problems with poor quality hair or alopecia. Hair colour shows a normal distribution.

EYE

The incidence of eye involvement is difficult to ascertain as most ocular changes are not severe and might well be missed without very detailed examination. Squints occur in over one-third of patients, often in association with refractive errors, and it is these features which are responsible for most of the unilateral visual impairment in IP, albeit of a mild degree. The hallmark of ocular IP involves abnormalities of the developing retinal vessels and the underlying pigmented cells, and is present in over 40% of patients. Areas of retinal ischaemia promote new vessel proliferation with subsequent bleeding and fibrosis, somewhat similar to that found in retinopathy of prematurity. This process generally aborts spontaneously at an early stage, but in 10% of patients may progress to gross intraocular scarring with severe visual loss. Fortunately, this usually affects only one eye and appears to be even less common in those without neurological abnormalities. Other notable associations include microphthalmos, cataract, and optic atrophy, but despite all this over 90% of patients have normal vision.

DENTAL

The dental features of IP occur in over 80% of cases and are of considerable diagnostic importance because, in contrast to many of the dermatological features, they persist through life. Either or both deciduous and permanent dentition may be affected and the typical features include hypodontia, delayed eruption, impaction, and malformation of the crowns, especially conical forms and accessory cusps.[28] (fig 9). Delayed eruption seems to be consistent but the explanation for this is unclear.

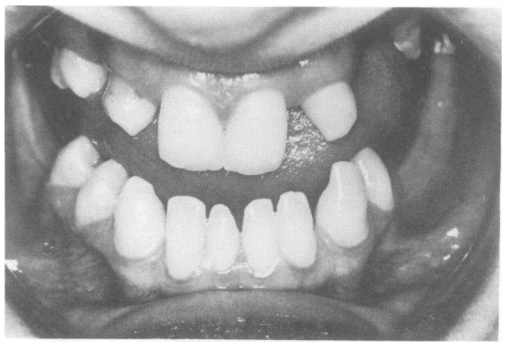

Figure 9 This 26 year old shows hypodontia, conical lower incisors, and retained deciduous teeth. There are no enamel defects.

There is no increased incidence of enamel hypoplasia and the teeth are of normal quality.

BREAST

Breast hypoplasia has been reported inconsistently, but breast anomalies are not mentioned in Carney's review.[17] In the authors' experience the incidence of breast anomalies, including (in order of frequency) supernumerary nipple, nipple hypoplasia, breast hypoplasia or aplasia (fig 10), and abnormalities in nipple pigmentation, is at least 10 times greater than the incidence in the general population.

NEUROLOGICAL

The neurological features described are diverse and Carney[17] found that 30% of the patients (465) in the reports he reviewed, that had adequate information, had notable CNS disease. A list of the commoner features he found includes convulsive disorders (13%),

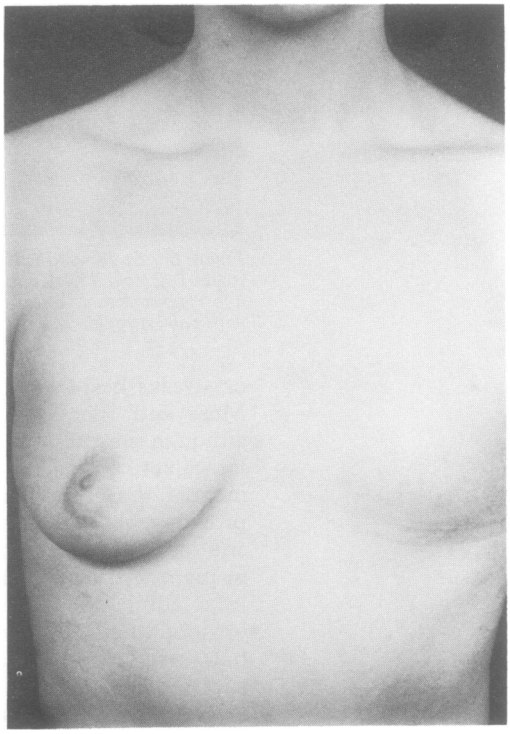

Figure 10 Unilateral breast aplasia is a well recognised but uncommon feature of IP.

Table 1 Diagnostic criteria for incontinentia pigmenti.

No evidence of IP in a first degree female relative	Evidence of IP in a first degree female relative
Major criteria	
Typical neonatal rash	The diagnosis of IP is likely in a first degree female relative of an affected female if any of the following features are demonstrable, alone or in combination
Erythema	
Vesicles	
Eosinophilia	
Typical hyperpigmentation	Suggestive history or evidence of typical rash
Mainly trunk	Skin manifestations of IP
Blaschko's lines	Hyperpigmentation
Fading in adolescence	Scarring
Linear, atrophic, hairless lesions	Hairless streaks
	Alopecia at vertex
	Anomalous dentition
	Woolly hair
	Retinal disease
	Multiple male miscarriages
Minor criteria (supportive evidence)	
Dental involvement	
Alopecia	
Woolly hair/abnormal nails	
Retinal disease	
At least one major criterion is necessary to make a firm diagnosis of sporadic incontinentia pigmenti. The minor criteria, if present, will support the diagnosis but because of their high incidence complete absence should induce a degree of uncertainty	

spastic paralysis (11%), motor retardation (7%), mental retardation (12%), and microcephaly (4%). Some of these features occurred concurrently. The clinical information in some of these reports is minimal with no mention of the typical skin manifestations or other ectodermal associations common in IP. It is possible that there may be cases of pigmentary mosaicism or similar disorders included in this review. More recent figures from our own study suggest that the incidence of CNS abnormalities is considerably less in familial IP and in cases where strict diagnostic criteria are applied (table 1). The overall incidence of mental or motor retardation in our series of over 100 subjects is less than 10%. Furthermore, in familial cases the incidence of severe mental retardation is only 3% compared to 15% in the sporadic group.

OTHERS

Skeletal anomalies, asymmetry, and ear anomalies have been reported as associations of IP but in our series all structural abnormalities were associated with severe neurological deficit and included contractures, dislocations, and scoliosis.

Patient management

SKIN

During the neonatal period, or whenever the blisters are present, strict attention to hygiene is paramount but specific treatment is not indicated. The lesions should be kept dry and protected from trauma. Reassurance that the rash will improve is most important. Later, when the rash is quiescent no special advice for skin care is necessary.

EYES

Retinal vascular changes have been documented as progressing during the first few months of life, and perinatal screening, repeated monthly during this period, is recommended. Xenon photocoagulation[37] or cryotherapy[23] have been shown to promote regression of neovascular changes in IP. Despite the paucity of data regarding this, such therapy would appear justified if the sight is threatened. In view of the high incidence of squint and amblyopia, screening should probably be continued for several years, particularly where there is a family history of squint.

TEETH

Parents should be warned that delayed eruption is common and that special dental attention may be necessary if teeth are missing or abnormal. Very few people with IP have major dental problems.

CENTRAL NERVOUS SYSTEM

CNS involvement in the neontal period is a poor prognostic sign and potential long term problems should be discussed. If there are no such features and no seizures (especially in familial cases) the child should be kept under careful review and the parents reassured. In our study all of the subjects with CNS disease had seizures in the neonatal period. One patient, with no mental or motor retardation, developed epilepsy in adolescence.

Confirmation of the diagnosis

The diagnosis of IP is founded on the clinical features. The classical florid rash of IP is diagnostic but unusual presentations can occur when skin biopsy may be necessary. In older children and adults with 'burnt out' IP, or in those who may be at risk of IP, designation of carrier status may be more difficult.

Features of IP in adults can be subtle and special techniques may be needed. A Wood's light is useful to show minor pigmentary anomalies.

Skin biopsy should always be considered in atypical or mentally retarded cases to look for chromosomal mosaicism.

The diagnosis may be inferred in an 'at risk' subject if there are typical dental anomalies, nail dysplasia, patchy alopecia, or retinal dysplasia without the typical skin involvement.

X inactivation studies in several centres[37–40] (Curtis, personal communication) have shown preferential inactivation of the maternal X in carriers of familial IP and skewed X inactivation in sporadic cases. This may well provide accurate prediction of carrier status in at risk subjects long before the gene is identified.

Differential diagnosis

Any condition exhibiting Blaschko's lines may be confused with IP and strict diagnostic criteria are crucial (tables 1 and 2). The skin changes in early infancy must be distinguished from epidermolysis bullosa, bullous impetigo, dermatitis herpetiformis, and herpes zoster. Focal dermal hypoplasia should not be confused with neonatal IP even in its severest form.

Table 2 Clinical features that may indicate an alternative diagnosis.

Skeletal involvement (other than that secondary to neurological deficit)
Gross neurological deficit
Asymmetry
Severe alopecia
Atypical hyperpigmentation
Gross hypopigmentation
Follicular pitting

X linked chondrodysplasia punctata also exhibits Blaschko's lines but there are certain, relatively constant, features which also occur in this disorder to distinguish it from IP, namely, skeletal dysplasia, congenital cataract, and alopecia. The typical scarring with follicular pitting seen in this condition is not seen in IP (fig 11). Naegli syndrome is a rare disorder characterised by reticular pigmentation of the skin but has no inflammatory phase. Other features include heat intolerance and palmar hyperkeratosis which are not features of IP.

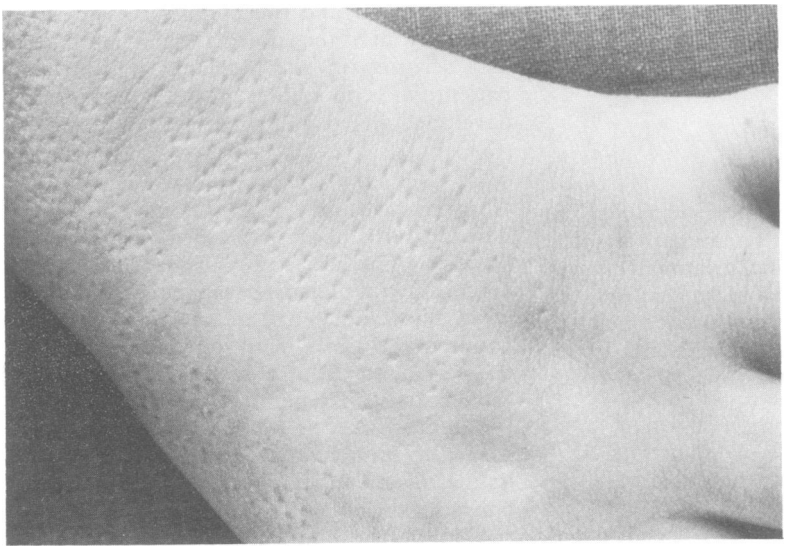

Figure 11 Linear scarring with follicular pitting seen in X linked chondrodysplasia punctata.

The heterogeneous group of disorders known as hypomelanosis of Ito (HI) or pigmentary mosaicism, now known to be the result of chromosomal mosaicism in some cases and assumed to be the result of single gene mosaicism in others[41–46] may be confused with IP. The clinical findings in HI include depigmentation (skin histology shows paucity of melanin granules in the basal layer of the epidermis) following Blaschko's lines and a high frequency of mental retardation, seizures, asymmetry, and skeletal abnormalities. The confusion with IP may be an important factor in the discrepancy between the previously predicted complication rates in IP and the complication rates found in our series.

Clearly, making a definitive diagnosis in cases with pigmentary anomalies is difficult but an important rule of thumb is to abide by strict diagnostic criteria and to avoid labelling a condition without a degree of certainty.

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